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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/762,294	04/02/2001	Chil-Yong Kang	9611-16	4835

1059 7590 06/29/2004

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EXAMINER

PARKIN, JEFFREY S

ART UNIT	PAPER NUMBER
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1648

DATE MAILED: 06/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/762,294	KANG ET AL.	
	Examiner	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 03 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 February 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-7 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-7 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Response to Amendment

Status of the Claims

Acknowledgement is hereby made of receipt and entry of the amendment filed 18 February, 2004, wherein claims 8-30 were canceled without prejudice or disclaimer and claims 1-7 amended. Claims 1-7 are currently under examination.

35 U.S.C. § 112, Second Paragraph

Claims 1-7 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Contrary to applicants' assertions, the claims still reference a "non-cytolytic" recombinant virus (i.e., "an essentially non-cytolytic signal sequence" which remains vague and indefinite. It is not readily manifest what constitutes an "essentially non-cytolytic" sequence. For instance, the prior art attributes different types of "cytolytic" activities to the HIV-1 Env. For instance, Stevensen et al. (1988) reported that cells expressing the HIV-1 Env had a "cytolytic-resistant" or non-cytopathic phenotype. Siliciano et al. (1988) reported that CD4⁺ gp120-specific clones manifest cytolytic activity and lyse uninfected autologous CD4⁺Ia⁺ T cells in the presence of gp120. Weinhold et al. (1989) demonstrated that HIV-1 gp120 can have both cytolytic and non-cytolytic properties depending upon the milieu and properties measured. Jassoy and colleagues (1993) also measured CD8⁺ HIV-1 Env-specific cytolytic responses. Moreover, it is not clear if other terms are encompassed by the claim language as well. For instance, overexpression of the enveloped glycoprotein in certain expression systems lead to cellular cytotoxicity. Other properties attributable to the HIV-1 Env include apoptosis, which causes cytolysis in the affected cell (Banda et al., 1992; Laurent-Crawford et al., 1993). Thus, the precise characteristics of the envelope glycoprotein referenced need to be

clearly set forth and defined. Moreover, it is not readily manifest how the viral envelope would be "essentially cytolytic". It either induces cytolysis or it doesn't. Appropriate correction is required. Perusal of the disclosure failed to clarify this issue. Although it is noted on p. 2 that the apoptotic properties of the HIV-1 Env may have been attributed to the signal sequence. Applicants should amend the claim language to more accurately identify the salient characteristics of the claimed invention (i.e., A modified recombinant human immunodeficiency virus type 1 (HIV-1) that does not induce apoptosis in infected cells wherein said virus has been modified to ...).

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The previous rejection of claims 8-21 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, is moot in view of applicants' amendment.

Claims 2-4, 6, and 7 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *In re Rasmussen*, 650 F.2d 1212, 211 U.S.P.Q. 323 (C.C.P.A. 1981). *In re Wertheim*, 541 F.2d 257, 191 U.S.P.Q. 90 (C.C.P.A. 1976). *In re*

Rochester, 358 F.3d 916, 69 U.S.P.Q.2d 1886 (C.A.F.C. 2004). To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Vas-Cath, Inc., v. Mahurkar*, 935 F.2d at 1563, 19 U.S.P.Q.2d at 1116.

The issue raised in this application is whether the original application provides adequate support for the broadly claimed genus of modified signal sequences. Specifically, the claims reference a **"modified" HIV-1 gp120 signal sequence** wherein **"no more than one positively charged amino acid"** is present or **"zero positively charged amino acids"** are present. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 U.S.P.Q.2d 1961, 1966 (Fed. Cir. 1997). The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the biomolecule of interest. *In re Bell*, 991 F.2d 781, 26 U.S.P.Q.2d 1529 (Fed. Cir. 1993). *In re Deuel*, 51 F.3d 1552, 34 U.S.P.Q.2d 1210 (Fed. Cir. 1995). A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 U.S.P.Q.2d 1895, 1905 (Fed. Cir. 1995). The court noted in this decision that a "laundry list" disclosure of every

possible moiety does not constitute a written description of every species in a genus because it would not reasonably lead those skilled in the art to any particular species.

An applicant may show possession of an invention by disclosure of drawings or structural chemical formulas that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole. An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. For some biomolecules, examples of identifying characteristics include a nucleotide or amino acid sequence, chemical structure, binding affinity, binding specificity, and molecular weight. The written description requirement may be satisfied through disclosure of function and minimal structure when there is a well-established correlation between structure and function. Without such a correlation, the capability to recognize or understand the structure from the mere recitation of function and minimal structure is highly unlikely. In the latter case, disclosure of function alone is little more than a wish for possession; it does not satisfy the written description requirement. *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1566, 43 U.S.P.Q.2d 1398, 1404, 1406 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089 (1998). *In re Wilder*, 736 F.2d 1516, 1521, 222 U.S.P.Q. 369, 372-3 (Fed. Cir. 1984). Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention.

As set forth *supra*, the claims reference a "modified" HIV-1 gp120 signal sequence wherein "no more than one positively charged amino acid" is present or "zero positively charged amino acids" are present. However, the disclosure fails to clearly set forth the amino acids that comprise the HIV-1 signal sequence. The disclosure clearly fails to identify the molecular determinants modulating the "non-cytolytic" properties of the virus. Thus, it is not readily manifest to the skilled artisan which amino acids are critical for the desired properties of the signal sequence. The disclosure also does not describe the preparation and characterization of a single HIV-1 gp120 signal sequence mutant. Thus, the skilled artisan cannot readily envisage the final product because of the inordinate number amino acid additions, subtractions, or modifications that the claim language allows. Moreover, nothing in the disclosure leads the skilled artisan to any particular mutant. Therefore, the skilled artisan would reasonably conclude that applicants were not in possession of the claimed invention at the time of filing. Applicants are reminded that the courts have concluded that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." *Brenner v. Manson*, 383 U.S. 519, 536 [148 U.S.P.Q. 689] (1966).

Claims 1-7 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not reasonably enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. As previously discussed, the claims are directed toward recombinant human immunodeficiency viruses bearing an "essentially non-cytolytic signal sequence". Additional limitations specify that the HIV-1 signal sequence has been modified to contain no more than one positively charged amino acid or none at all. The disclosure details the production of two recombinants wherein the HIV-1 gp160 signal sequence was replaced

with either the mellitin signal sequence (MSS) or the interleukin-3 signal sequence (ILSS). Appropriately drafted claim language directed toward these embodiments would be acceptable. No HIV-1 signal sequence mutants are described in the disclosure.

The legal considerations that govern enablement determinations pertaining to undue experimentation have been clearly set forth. *Enzo Biochem, Inc.*, 52 U.S.P.Q.2d 1129 (C.A.F.C. 1999). *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988). *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

Inadequate Direction/Guidance Provided

The disclosure fails to provide adequate guidance pertaining to the molecular determinants modulating the biological properties of the HIV-1 signal sequence. Thus, it is not known to the skilled artisan which amino acid residues are critical for maintaining the desired characteristics of the signal sequence (i.e., non-cytolytic). Accordingly, the skilled artisan could not reasonably ascertain which amino acid additions, deletions, or substitutions should be performed on the parent sequence. Moreover, the disclosure does not lead the skilled artisan to any particular amino acid residues.

Absence of Working Embodiments

The disclosure fails to provide any working embodiments wherein modified HIV-1 gp120 signal sequence mutants were prepared and their biological properties assessed. Thus, the skilled artisan

has been asked to guess as to which amino acid additions, deletions, or substitutions will produce a "non-cytolytic" signal sequence.

State-of-the-Art

The state-of-the-art vis-à-vis the molecular determinants modulating the cytolytic properties of the HIV-1 gp120 signal sequence is one of unpredictability. The prior art does not provide any guidance pertaining to those regions of the signal sequence that are required for the claimed biological properties of the virus. Moreover, it has been well-documented in the prior art that single or multiple amino acid additions, deletions, or modifications can have a profound effects on the peptide properties. Thus, absent sufficient guidance concerning suitable modifications to be made, the skilled artisan cannot reasonably predict which modifications will be appropriate.

Excessive Experimentation Required

The claims encompass a large number of mutants (i.e., single or multiple amino acid additions, substitutions, or deletions). If one argues that the signal sequence is approximately 30 amino acids in length, the claims could potentially encompass more than 20^{30} different combinations. Thus, undue experimentation would clearly be required to synthesize these modified signal sequences, prepare recombinant viruses containing them, and examine their affects on apoptosis.

Excessive Claim Breadth

As set forth above, the claims encompass a potentially large genus of mutant signal sequences. However, the disclosure clearly fails to provide sufficient guidance pertaining to the molecular determinants modulating the biological properties of the signal sequence. Therefore, the disclosure is clearly inadequate to support the full breadth of the claimed invention.

Accordingly when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Li et al. (1994). Li and colleagues disclose the preparation of recombinant HIV-1 viruses wherein the wildtype gp160 signal sequence has been replaced with the MSS or IL-3SS (see ABSTRACT, p. 256). This publication also discloses the preparation of recombinant HIV-1 viruses wherein the positive charge of the HIV-1 signal sequence has been reduced to contain no more than zero or one positively charged amino acids (see pp. 271-272). Thus, this teaching meets all of the claimed limitations.

Claims 1 and 5 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Li et al. (1996). Li and colleagues disclose the preparation of recombinant HIV-1 viruses wherein the wildtype gp160 signal sequence has been replaced with the mellitin signal sequence or interleukin-3 signal sequence (see ABSTRACT, p. 9606). Thus, this teaching meets all of the claimed limitations.

35 U.S.C. § 103(a)

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to

be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 6 and 7 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Li et al. (1994) in view of Daniel et al. (1992). Li and colleagues disclose the preparation of recombinant HIV-1 viruses wherein the wildtype gp160 signal sequence has been replaced with the MSS or IL-3SS (see ABSTRACT, p. 256). This publication also discloses the preparation of recombinant HIV-1 viruses wherein the positive charge of the HIV-1 signal sequence has been reduced to contain no more than zero or one positively charged amino acids (see pp. 271-272). The preparation of *nef*-deficient avirulent viruses is not disclosed. Daniel et al. (1992) teach that *nef*-deficient SIV produces a virus that is replication-impaired and apathogenic. Furthermore, vaccine compositions comprising this virus protected macaques against viral infection. Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to

prepare recombinant HIV-1 viruses with modified signal sequences, as taught by Li et al. (1994), and to further include a *nef*-deletion in the construct, as provided by Daniel et al. (1992), since this would provide a recombinant virus that is replication-impaired and expressed to high quantities. The skilled artisan would be motivated to prepare such a construct because of obvious safety considerations (i.e., the virus would obviously be safer to handle in manufacturing viral antigens for diagnostic assays).

Claims 6 and 7 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Li et al. (1996) in view of Daniel et al. (1992). Li and colleagues disclose the preparation of recombinant HIV-1 viruses wherein the wildtype gp160 signal sequence has been replaced with the MSS or IL-3SS (see ABSTRACT, p. 9606). The preparation of *nef*-deficient avirulent viruses is not disclosed. Daniel et al. (1992) teach that *nef*-deficient SIV produces a virus that is replication-impaired and apathogenic. Furthermore, vaccine compositions comprising this virus protected macaques against viral infection. Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to prepare recombinant HIV-1 viruses with modified signal sequences, as taught by Li et al. (1996), and to further include a *nef*-deletion in the construct, as provided by Daniel et al. (1992), since this would provide a recombinant virus that is replication-impaired and expressed to high quantities. The skilled artisan would be motivated to prepare such a construct because of obvious safety considerations (i.e., the virus would obviously be safer to handle in manufacturing viral antigens for diagnostic assays).

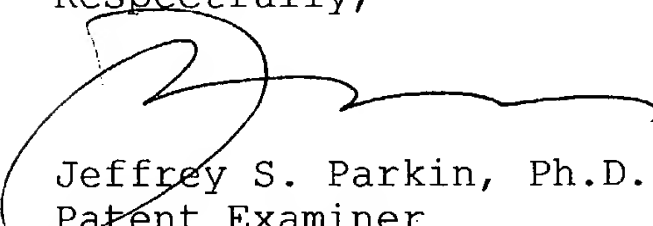
Correspondence

Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (571) 272-0908. The examiner can normally be reached Monday through Thursday from 9:30 AM to 7:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful,

the examiner's supervisors, Laurie Scheiner or James Housel, can be reached at (571) 272-0910 or (571) 272-0902, respectively. Direct general inquiries to the Technology Center 1600 receptionist at (571) 272-1600.

Formal communications may be submitted through the official facsimile number which is (703) 872-9306. Hand-carried formal communications should be directed toward the customer window located in Crystal Plaza Two, 2011 South Clark Place, Arlington, VA. Applicants are directed toward the O.G. Notice for further guidance. 1280 O.G. 681. Informal communications may be submitted to the Examiner's RightFAX account at (571) 273-0908.

Respectfully,



Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1648

24 June, 2004